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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,500	07/24/2006	Roderick H. Scott	ABLE-0027	9312

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EXAMINER
ARIANI, KADE

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
10/17/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/561,500	SCOTT ET AL.	
	Examiner	Art Unit	
	KADE ARIANI	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on July 03, 2008, has been received and entered.

Claims 30-63 are pending in this application and were examined on their merits.

Claim Objection

The objection to claims 30, 38-40 are withdrawn due to Applicant's amendments to the claims filed on 07/03/2008.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of Claims 44-46 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn due to Applicant's amendments to the claims filed on 07/03/2008.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 30-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Malovrh et al. (Comparative Biochemistry and Physiology, Part C, 1999, p.221-226).

Claims 30-34 are drawn to a composition comprising a reversible pore-forming sponge toxin, sponge toxin comprises poly-APS, sponge toxin is obtained form *Reniera sarai*, wherein the sponge toxin has a molecular weight between 5.0 kDa to 20 kDa.

Malovrh et al. disclose a composition comprising a sponge toxin, sponge toxin comprises poly-APS, sponge toxin is obtained form *Reniera sarai*, wherein the sponge toxin has a molecular weight between 5.0 kDa to 20 kDa (p. 221, Abstract and Introduction 1st column, p. 222 Fig.1a.).

Malovrh et al. is silent about that the pore-forming property of the sponge toxin is reversible. However, the prior art composition is the same as the claimed composition and thus must necessarily exhibit the reversible pore-forming properties.

Malovrh et al. therefore clearly anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 30-40, and 60-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malovrh et al. (Comparative Biochemistry and Physiology, Part C, 1999, p.221-226).

Claims 30-40, and 60-63 are drawn to a composition comprising a reversible pore-forming sponge toxin, sponge toxin comprises poly-APS, sponge toxin is obtained form *Reniera sarai*, wherein the sponge toxin has a molecular weight between 5.0 kDa to 20 kDa, the concentration of sponge toxin is between 0.5 ng/ml and 0.5 µg/ml, and a method for reversible formation of membrane pores, comprising the steps of a) incubating the membrane in the presence of composition comprising a sponge toxin, b) removing the composition from contact with the membrane, and addition of zinc solution (concentration is between 1 to 2 mM, 1.5mM).

As mentioned immediately above, Malovrh et al. teach a composition comprising a sponge toxin, sponge toxin comprises poly-APS, sponge toxin is obtained form *Reniera sarai*, wherein the sponge toxin has a molecular weight between 5.0 kDa to 20 kDa, the concentration of sponge toxin is between 0.5 ng/ml and 0.5 µg/ml (p. 221, Abstract and Introduction 1st column, p. 222 Fig.1a., and p.223 Fig.3.). Malovrh et al. further teach a method for reversible pore formation (divalent cation (Zn^{2+})-mediated inhibition of pore formation after poly-APA induced hemolysis) comprising the steps of incubating the membrane in the presence of composition comprising a sponge toxin, addition of zinc solution, and the concentration of zinc solution is between 0 to 1 mM (p.222 1st column, 2.2, and 2nd column 4th paragraph 2.5.). Malovrh et al. teach we

suggest that the fact and the ability of Zn^{2+} to inhibit already progressing lysis suggest that divalent cations close the resulted pores (p.225 1st column 2nd paragraph).

Malovrh et al. do not teach removing the composition from contact with the membrane. However, removing a substrate from a reaction mixture is within the capability of a person with ordinary skill in the art.

Therefore, it would have been obvious to one of ordinary skill in the art to modify the method as taught by Malovrh et al. by adding a step of removing the composition comprising sponge toxin from the contact with the membrane and provide a method for reversible pore formation The motivation would be to control the degree of pore formation in the membranes by sponge toxin.

Claims 41-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woude et al. (in IDS, PNAS, 1997, Vol. 94, p.1160-1165) in view of Malovrh et al. (Comparative Biochemistry and Physiology, Part C, 1999, p.221-226).

Claims 41-49 are drawn to a method for transfection of a macromolecule into a cell *in vitro*, the method comprising the steps of: a) incubating the cell in the presence of a composition comprising a sponge toxin, b) removing the composition from contact with the cell; and c) adding a macromolecule, the macromolecule is cDNA, the cell is incubated in the presence of the composition for 5 minutes, prior to the addition of the macromolecule, the composition and macromolecules are removed and replaced with standard media, cells are incubated for 180 minute.

Woude et al. teach a method for transfection of a macromolecule into a cell *in vitro*, comprising the steps of: a) incubating the cell in the presence of a composition comprising a pyridinium compound, removing the composition from contact with the cell, adding a macromolecule, the macromolecule is cDNA, prior to the addition of the macromolecule, the composition and macromolecules are removed and replaced with standard media (Abstract and p.1161, 2nd column 5th paragraph).

Woude et al. further teach pyridinium compounds have been developed that display highly efficient DNA transfection properties. The transfection efficiency of several of these compounds is enhanced by an order of magnitude when compared with the transfection efficiency accomplished with the widely used cationic lipid system, lipofectin. Most importantly, the pyridinium compounds were found to be essentially nontoxic toward cells (Abstract).

Woude et al. do not teach transfection in the presence of poly-APS (pyridinium compound), and the claimed incubation times. However, Malovrh et al. teach a composition comprising a sponge toxin, a pyridinum compound, polymeric alkylpyridinium (poly-APS), obtained form *Reniera sarai*. Malovrh et al. further teach the hemolytic activity (pore forming) of poly-APS is due their detergent-like structure and behavior in aqueous solutions.

Moreover, routine experimentation is widely used by one of ordinary skill in the art to determine optimum or workable ranges of particular parameters such as incubation time, and concentration of reagents in a transfection assay. “[W] here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover

the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (MPEP Chapter 2100 – p.141).

Therefore, it would have been obvious to one of ordinary skill in the art to substitute the pyridinium compound in the transfection method as taught by Woude et al. with the pyridinium compound (poly-APS) as taught by Malovrh et al. with predictable results to provide a method for transfection of a macromolecule into a cell *in vitro*, because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Claims 50-59 are rejected are rejected under 35 U.S.C. 103(a) as being unpatentable over Woude et al. (PNAS, 1997, Vol. 94, p.1160-1165) and Arendt et al. (Neuroscience, 1998, Vol. 85, No.4, p.1337-1340) in view of Ballard C.G. (European Neurology, 2002, Vol. 47, p.64-70) and further in view of Bunc et al. (Toxicon, 2002, Vol. 40, p.843-849).

Claims 50-53 are drawn to a method for transfection of a macromolecule into a cell *in vivo*, the method comprising the steps of: a) incubating the cell in the presence of a composition comprising a sponge toxin and a macromolecule, the macromolecule is the cytoskeletal protein tau, and hippocampal neurone.

Claims 54-59 are drawn to a rodent model and a method of studying a neurological disease comprising applying a composition comprising a sponge toxin, tau protein, and phosphatase inhibitor, to the hippocampus of a rodent, the phosphatase inhibitor is okadaic acid.

As mentioned immediately above, Woude et al. teach a method for transfection of a macromolecule into a cell using pyridinium compounds.

Woude et al. further teach oligonucleotide and /or gene therapy are promising approaches not only in the treatment of diseases with a genetic defect, but also in developing therapeutic strategies for diseases such as cancer, infectious disease, and acquired diseases. Vesicles composed of cationic synthetic amphiphiles have been developed for the delivery of genes *in vitro,* as well as *in vivo*. Nucleic acids associate with amphiphiles in a highly efficient manner, and protocols for preparation and delivery are simple, the transfection efficiencies are usually better, however, a major drawback of synthetic amphiphiles has been the severe cellular toxicity of such compounds (p. 1160 Introduction 1st and 2nd columns).

Woude et al. do not teach sponge toxin (poly-APS). However, Bunc et al. teach effects of poly-APS isolated from *Reniera sarai*, in rat. Bunc et al. also teach, poly-APS is a potent acetylcholinesterase inhibitor, and the acetylcholinesterase inhibitory effects are not responsible for the lethal activity of the toxin (Abstract and p.847, 1st column lines 2-5).

Woude et al. do not teach the cytoskeletal protein tau, and hippocampal neurone. However, Arendt et al. teach a rodent model and a method of studying a neurological disease comprising applying okadaic acid to the cerebral cortex of a rodent (p.1337, 2nd column, p.1338, 1st column and Fig.1.).

Arendt et al. further teach one major abnormalities in AD are made up by the microtubule-associated protein tau in a hyperphosphorylated form (p.1337, 1st column).

Arendt et al. also teach okadaic acid applied either by single local injection or by chronic intraventicular infusin into rat brain induces a hyperphosphorylated state of tau at some of those sites that are found to be hyperphosphorylated in tau preparation obtained from Alzheimer's disease (AD) brains (p.1337, 2nd column 3rd paragraph).

Further motivation is in, Ballard who teaches therapeutic approaches in the treatment of Alzheimer's disease (AD) were developed with the aim of enhancing cholinergic function, the most successful of which has been the use of cholinesterase inhibitors (Abstract tan dp.65, 1st column 2nd paragraph).

Therefore, in view of the above teachings, it would have been obvious to one of ordinary skill in the art to substitute the transfection agent in the transfection method of Woude et al. with a composition comprising sponge toxin (pyridinium compound) as taught by Bunc et al. to provide a method for transfection of a macromolecule *in vivo*, because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Moreover, since, at the time the invention was made it was well known in the art that among the therapeutic approaches in the treatment of Alzheimer's disease (AD) the use of cholinesterase inhibitors has been the most successful, therefore a person of ordinary skill in the art would have been motivated to modify the method of Arendt et al. by applying a sponge toxin, a potent acetylcholinesterase inhibitor, as taught by Bunc et al. to provide a method of studying a neurological disease with predictable results.

Response to Arguments

Applicant's arguments filed on 07/03/2008 have been fully considered but they are not persuasive.

Applicant argues that Malovrh does not teach that the polymeric alkylpyridinium salts isolated from the marine sponge form *Reniera sarai* are reversible pore-forming toxins, and Malovrh polymeric alkylpyridinium salts behave in a different manner to the instant claimed sponge toxins. Applicant argues that in the formation of reversible pores was attenuated by Zn2+ in the present invention, i.e. prevented from forming when Zn2+ was added after poly-APS had no (lines 33 page 31 to line 32 page 32 of the instant specification).

However, lines 33 page 31 to line 1 page 32 of the instant specification, recite "the hemolytic actions of poly-APS have been found to be attenuated by zinc, most likely in the ionic form Zn2+", and Malovrh disclose hemolysis induced by poly-APS is inhibited by Zn2+. Therefore, Malovrh' composition is the same as the claimed composition because Malovrh' sponge toxin possess the characteristic of the claimed composition.

Moreover, i.e. lines 16-18 page 32 of the instant specification, discuss the results of poly-APS on membrane potential (a different protocol), and disclose, "once poly-APS had produced pores or lesions in the cell membrane zinc failed to attenuate the conductances" and does not discuss the effect of Zn2+ added after poly-APS on the already formed pores, and this cannot be opposite to Malovrh, because Malovrh does

not disclose experimental protocols with poly-APS and Zn2+ effects on membrane potential and conductivity.

Applicant argues that the poly-APS of Malovrh is not suitable for transfection because the membrane permeabilization which Malovrh et al. induce is not reversible and results in cell death. However, as mentioned immediately above, the method of pore formation taught by Malovrh et al. is reversible. Malovrh et al. teach that the fact and the ability of Zn^{2+} to inhibit already progressing lysis suggest that divalent cations close the resulted pores (p.225 1st column 2nd paragraph).

Applicant argues that the person of ordinary skill in the art would not have been motivated to combine the prior art to achieve the claimed invention with reasonable expectation of success.

However, all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. KSR, 550 U.S. at ___, 82 USPQ2d at 1395; Sakraida v. AG Pro, Inc., 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); Anderson 's-Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp., 340 U.S. 147, 152, 87 USPQ 303, 306 (1950). "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." KSR, 550 U.S. at ___, 82 USPQ2d at 1396.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kade Ariani whose telephone number is (571) 272-6083. The examiner can normally be reached on 9:00 am to 5:30 pm EST Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status

information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kade Ariani
Examiner
Art Unit 1651

/Leon B Lankford/
Primary Examiner, Art Unit 1651